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CRITICAL REVIEW

Status epilepticus in older adults: A critical review

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Abstract

Older adults (≥60 years of age) have the highest incidence of status epilepticus (SE) among adults and experience the highest morbidity and mortality. SE incidence increases with age in adulthood. A recent study from Austria estimated an incidence of 89.6/100 000 and 67.6/100 000 person-years adjusted for age and sex in women and men aged >60 years, respectively, compared to 18.1/100 000 in adults aged <60 years. In-hospital mortality associated with SE increases fourfold from the 3rd to 9th decade of life. There are multiple important considerations unique to older adults. Etiologies, including ischemia, hemorrhage, and neoplasm, are more common in older adults and are independently associated with poorer outcomes. Important physiological changes of aging affect both the pharmacokinetics and pharmacodynamics of established treatments for SE. Pharmacology studies have shown differences in sensitivity to benzodiazepines and benzodiazepine elimination, as well as greater unpredictability of antiseizure medications such as phenytoin. Older adults have been largely underrepresented in high-quality randomized clinical trials of SE treatment relative to the incidence of SE in this population. The Established Status Epilepticus Treatment Trial published a post hoc analysis of older adults that showed similar efficacy of treatments, although many older trials did not stratify by age, limiting the opportunity to recognize age-related differences in efficacy and safety. Future research should be aimed at investigating treatment selection and dosing in older adults with SE.

KEYWORDS

aging, antiseizure medications, benzodiazepines, pharmacology, status epilepticus

1 | INTRODUCTION

The incidence of status epilepticus (SE) increases with advancing age and is associated with increased morbidity and mortality. Clinicians managing SE in older adults must be aware of the unique differences in presentation, etiology, treatment, and prognosis in this population. SE is a resource-intensive condition often requiring critical

Emily L. Johnson and Emily J. Gilmore are co-last authors.

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care; the median cost of hospitalization reached $25 000 USD in 2018, with annual costs approaching $4 billion.[1] Overall mortality has not changed over the past 3 decades, but emerging literature suggests that it may be increasing in the elderly.[2] With the aging population, cases of SE are expected to rise. In this review, we will examine the current evidence guiding SE treatment in older adults and identify gaps in knowledge and recommendations as opportunities for further inquiry.

Key points

- Among adults, status epilepticus incidence, morbidity, and mortality increase with age.
- Changes in neurotransmitter signaling and amyloid deposition in older adults may increase the risk for seizure and status epilepticus.
- Pharmacokinetic and pharmacodynamic changes of aging impact the efficacy and elimination of SE treatments and sensitivity to toxicity.
- Older adults are underrepresented in randomized clinical trials of first- and second-line treatment.
- Future investigation into the clinical impact of pharmacokinetic and pharmacodynamic changes of SE treatment may improve SE management in older adults.

2 | MATERIALS AND METHODS

We searched PubMed from inception to September 1, 2024 using combinations of the terms "status epilepticus", "older adults", "aging", and "elderly" without language restrictions. We combined "older adults", "aging", and "elderly" with benzodiazepines, antiseizure medications (ASMs), continuous intravenous anesthetic drugs (CIVADs), and other SE treatments. Treatments were also combined with "pharmacokinetics" and "pharmacodynamics". We hand-searched reference lists of articles retrieved to find additional studies. We prioritized articles published within the past 10 years as able, but also selected publications to highlight areas of interest, including review articles.

3 | DEFINITIONS AND INCIDENCE

The definition of "older adult" varies, although the ages of 60 or 65 years are commonly applied cutoffs when examining demographics of SE.[3] We report age ranges from the primary literature, as well as available stratifications. If unavailable, we identify the proportion of participants ≥65 years old. The terminology to describe SE, particularly SE exclusive of bilateral tonic–clonic SE, has evolved significantly over the past 30 years. As such, we use the term nonconvulsive SE (NCSE) to describe SE without prominent motor features (which may or may not have relied upon electroencephalography [EEG] for diagnosis) and for publications reporting NCSE based on the Salzburg criteria or earlier definitions.[4] We use the terms electrographic seizure (ESz) and electrographic SE (ESE) for recent studies that employ the 2021 American Clinical Neurophysiology Society criteria and in which ESz and ESE are detected with EEG monitoring.[5] SE incidence increases with age in adulthood. A recent study from Austria estimated an incidence of 89.6/100 000 and 67.6/100 000 person-years adjusted for age and sex in women and men aged >60 years, respectively, compared to 18.1/100 000 in adults aged <60 years.[6] The incidence of SE, including convulsive SE, nonconvulsive SE, and SE with prominent motor phenomena (including focal and myoclonic SE), increases dramatically with advancing age.[6] Comparatively, SE in older adults is more often nonconvulsive, and may be more refractory.[7]

4 | ETIOLOGY

Increased risk of SE is associated with acquired brain injury, infarction, hemorrhage, infection, neoplasm, and dementia, as well as susceptibility to systemic insults, for example, sepsis and metabolic derangements. Stroke, trauma, metabolic derangements, and dementia are common causes of SE in older adults, whereas ASM withdrawal and alcohol-related SE are less common etiologies.[8] Approximately 35% of older adults with SE have preexisting epilepsy, whereas nearly two thirds of cases are new onset SE.[9] A pooled study of nationwide inpatient sample databases including 130 109 adults 65 years and older with SE found acute ischemic stroke (11.2%), nontraumatic brain hemorrhage (5.4%), and malignant brain neoplasm (4.9%) as the most common etiologies, followed by epilepsy (3.8%) and acute traumatic brain injury (3.7%).[10] Sepsis, sodium imbalance, pneumonia, and hypoxic ischemic brain injury were commonly associated comorbidities.[10] Etiologies likely vary geographically, as evidenced by a higher incidence of central nervous system infection related SE in a national sample from South Korea; however, in this group, incidence of infectious etiology for SE decreased with age.[11]

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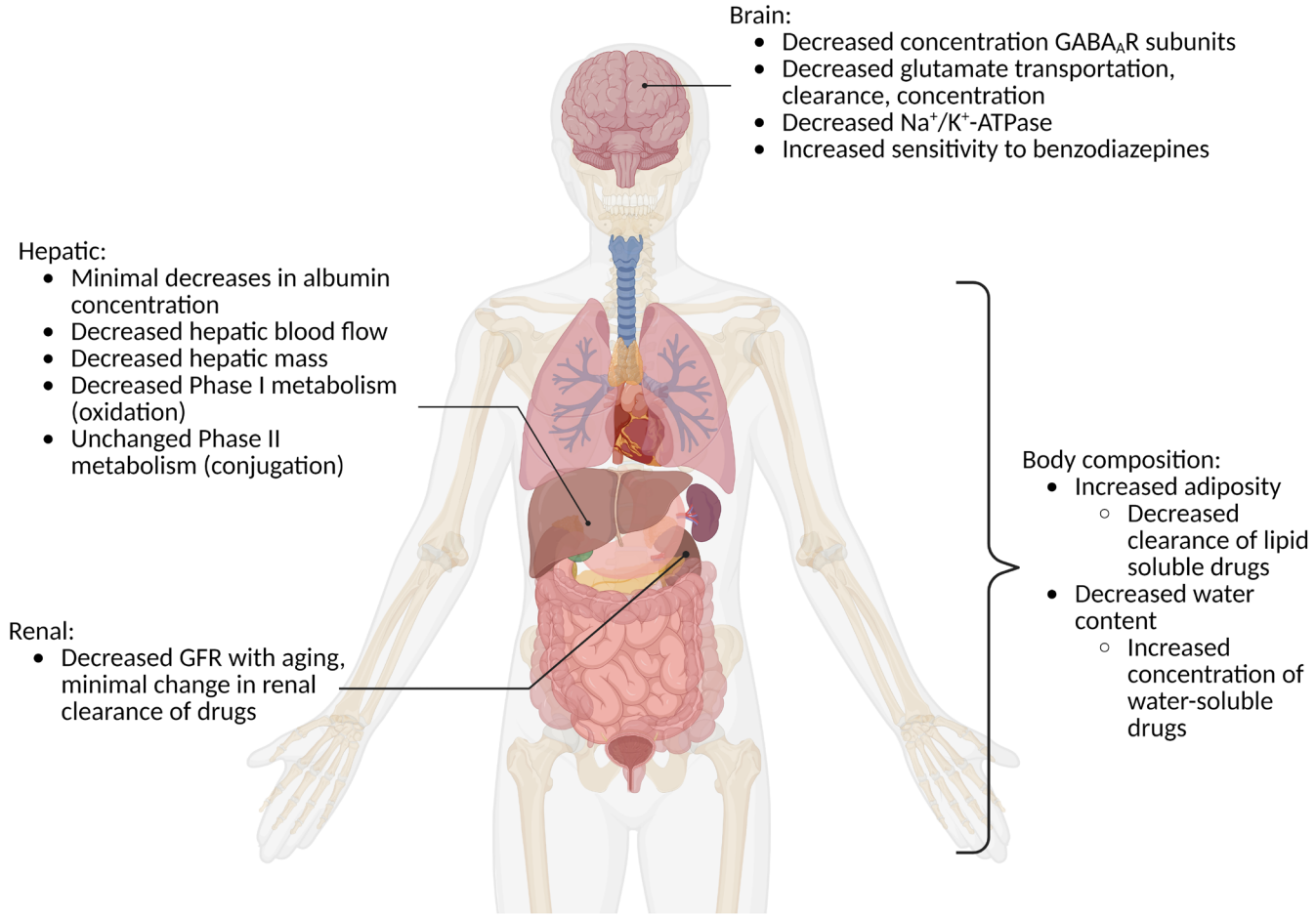

FIGURE 1 Age-related changes relevant to seizure pathophysiology and treatment pharmacology. GABA$_A$R, γ-aminobutyric acid type A receptor; GFR, glomerular filtration rate. Created in BioRender by M.R.W. (2025).

5 | PHYSIOLOGICAL CHANGES IN AGING

Physiological changes in aging inform the risk for SE and management strategy in older adults (Figure 1). Age-related changes in neuronal signaling that confer added risk of seizure and SE in older adults are an important, yet understudied area of inquiry and may elucidate why older adults are more likely to develop SE following acute brain injury than younger adults.

Seizure generation is related to excessive excitation or loss of inhibitory mechanisms.[12] Data regarding age-related changes in γ-aminobutyric acid (GABA) receptors are conflicting.[13] GABA receptor binding in rat brains does not decrease with age, yet chloride ion influx is altered in models.[14] Human studies suggest both age- and sex-related decreases in several GABA$_A$ receptor subunits, suggesting enhanced sensitivity to benzodiazepines in older adults.[8,15] There are reductions in astrocytic glutamate transporters and lower glutamate clearance, along with overall lower levels of glutamate, potentially resulting in lower seizure threshold.[16] These abnormalities, along with excessive glutamate receptor activation, are accentuated in neurodegenerative disease.[17] In SE, there is increased N-methyl-D-aspartate receptor (NMDAR) expression at the synapse, propagating neuroexcitation. In prolonged SE, NMDARs mediate synaptic remodeling, which further promotes excitotoxicity.[12] Prior brain cortical injury such as stroke or ischemia may modify the expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor and increase excitability.[18] Although the consequences of changes in the glutamatergic system associated with physiological aging have not been studied in seizures or SE in older adults, it is plausible that this population is more susceptible to neurotoxicity associated with prolonged seizures. Models suggest decreased Na^+/K^+-ATPase in the brains of aged rats, although its impact on seizure proclivity is unknown.[19] Although changes to GABA receptors and glutamate homeostasis are described in the brains of aging adults, their association with the development of late-life seizures and SE remains a knowledge gap in the field. Finally, increasing evidence from animal studies suggests that products of neurodegeneration, particularly amyloid and tau, are both increased by neuronal hyperexcitability and cause neuronal hyperexcitability, suggesting a

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bidirectional relationship between neurodegeneration and seizures.[20] Aged rat models suggest enhanced sensitivity to convulsive agents and neuronal network changes that increase epileptic vulnerabilty.[18] Pending better characterization of seizure formation in the aging brain, there is no evidence to suggest any single ASM is preferable for older adults.

There are several important aging-associated physiological changes relevant to drug absorption, pharmacokinetics, pharmacodynamics, and elimination. Decreased uptake of oral medications may decrease bioavailability of adjunctive therapies only available in oral formulations.[21] Albumin concentrations are decreased in malnutrition and acute illness and marginally decline with aging (≤20%; .5 g/L per decade). Reduction in albumin concentrations can result in heterogenous binding on the individual patient level. In addition, hepatic clearance of unbound drugs may increase in response to reductions in albumin binding.[22] As a result, extrapolation to the broader older adult population is challenging.

Increased body fat and decreased body water content lead to increased concentrations of water-soluble drugs and prolonged elimination of lipid-soluble drugs by up to 20%.[21] Sarcopenia may reduce absorption of intramuscular injections, such as midazolam.[23] Hepatic blood flow and liver mass significantly diminish with aging, which may reduce hepatic clearance of drugs.[21] Hepatic oxidative metabolism (phase I metabolism) is typically compromised in older persons, whereas conjugation (phase II metabolism) is mostly unaffected.[24] Although glomerular filtration rate decreases with age, clearance of renally excreted medications does not appear to diminish.[21] Older adults, however, are at increased risk for renal insufficiency and chronic kidney disease, potentially compromising elimination of renally cleared drugs. Overall adverse drug reactions correlate with increasing age and are a common cause of death in older hospitalized patients.[25] Pharmacodynamics, comorbidities, and concomitant treatments may therefore be more important considerations than pharmacokinetics or potential pathophysiological differences.

6 | MANAGEMENT

Current guideline-based management strategies for adults with SE are agnostic to age and are largely derived from studies of convulsive SE. In this section, we will discuss ASMs and adjunctive therapies used in SE management (Tables 1 and 2), as well as relevant age-related pharmacodynamic and pharmacokinetic adaptations. Only two trials have exclusively examined SE management in older adults to date.[26,27] With the exception of a phase I/II study of ketogenic diet (KD), we did not identify the use of upper age limits in any prospective study or retrospective analysis of SE treatment.[28]

6.1 | Benzodiazepines

The Veterans Affairs (VA) cooperative study, comparing intravenous lorazepam, phenytoin (PHT), phenobarbital, and diazepam plus PHT, enrolled patients with generalized convulsive SE (GCSE) as well as "subtle SE" (NCSE).[29] A post hoc analysis of patients aged ≥65 years demonstrated comparable response rates as the entire cohort (63% success of lorazepam in patients ≥65 years old with overt GCSE vs. 64.9% in all enrolled patients).[30] The Pre-Hospital Treatment Of Status Epilepticus Trial trial randomized 205 adults with SE to intravenous lorazepam, diazepam, or placebo and demonstrated superior seizure cessation and recovery of consciousness in the lorazepam group versus controls with a trend toward fewer respiratory or cardiovascular complications in the benzodiazepine groups (lorazepam: 10.6%, diazepam: 10.3%, placebo: 22.5%).[31] The mean age of participants was approximately 50.8 ± 19.1 years, including approximately 22%–23% aged ≥65 years, although no subgroup analyses were conducted. The Rapid Anticonvulsant Medication Prior to Arrival Trial compared administration of intravenous lorazepam 4 mg versus intramuscular midazolam 10 mg in a noninferiority trial of 893 participants with GCSE[32]; 20% of participants were ≥61 years old. From our review of the primary data, 13.8% of participants randomized were ≥65 years old. Intramuscular administration of midazolam decreased time to drug delivery and was noninferior to lorazepam, with response rates of 73.4 (95% confidence interval [CI] = 69.3–77.9) versus 63.4 (95% CI = 58.9–67.9), respectively. Treatment efficacy and risk for complications were not examined based on participant age.

Post hoc analysis of the Established Status Epilepticus Treatment Trial (ESETT), in which randomized participants received cumulative doses of at least 4 mg lorazepam or 10 mg midazolam, identified frequent benzodiazepine underdosing.[33] Only 13.3%, 17.9%, and 41.6% of first doses of lorazepam, midazolam, and diazepam, respectively, met American Epilepsy Society guidelines of 4, 10, and 10 mg, respectively. Compared with children, adults were more likely to receive doses below the guidelines. Older adults were not analyzed separately. Improvement of adequate benzodiazepine dosing may be important in improving outcomes in SE in older adults. Benzodiazepine doses less than guideline recommendations have been shown to be associated with a need for further rescue medications and for respiratory support, decreased likelihood of SE cessation, and progression to refractory SE (RSE), whereas overdosing

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TABLE 1 Medications used in status epilepticus.

Drug	Dose	Mechanism of action	Metabolism	Interactions	Adverse effects	Considerations for older adults
First line: benzodiazepines						
Clonazepam	• .015 mg/kg • IV • Typically 1 mg per dose	Allosteric modulator of $GABA_AR$, increasing frequency of Cl^- channel opening	• Hepatic (CYP3A4)	• Induced by carbamazepine, fos-/phenytoin, phenobarbital • Inhibited by: valproic acid • Midazolam inhibits: CYP3A4, 2C9, 2C8	• Hypotension • Respiratory depression • Short duration of effect for initial doses, may accumulate with repeated dosing • Diazepam and lorazepam contain propylene glycol	• Sedation achieved at lower doses • Decreased clearance of diazepam and midazolam • Heavily protein bound • Decreased clearance
Diazepam	• .15–.2 mg/kg • IV, PR • Max 10 mg per dose		• Hepatic (CYP2C19, CYP3A4) • Renal excretion			
Lorazepam	• .1 mg/kg • IV • Max 4 mg per dose		• Hepatic metabolism (glucuronidation)			
Midazolam	• .2 mg/kg, • IM, IN, IV • Max 10 mg		• Hepatic metabolism • Active metabolite undergoes renal excretion			
Second line: ASMs						
Fosphenytoin/phenytoin	• LD: 20 mg/kg PE • Max 1500 mg • MD: 100 mg TID	Modulates VGSC to prolong inactivation	• Fosphenytoin: prodrug converted to phenytoin via hepatic and erythrocyte phosphatases • Hepatic metabolism	• Induces CYP1A2, 2B6, 2C, 3A3, 3A4, 3A5, 3A6, 3A7 • Induces carbamazepine, phenobarbital • Induced by carbamazepine • Concentration increased by benzodiazepines	• Hypotension • Arrythmias • Neurotoxicity: nystagmus, ataxia • Purple glove syndrome (IV phenytoin)	• Increased risk of complications • Saturation of metabolic pathways at lower concentrations • Impaired free phenytoin with renal impairment
Lacosamide	• LD: 200–400 mg • MD: 100–200 mg BID	Enhances slow inactivation of VGSC	• Hepatic 60% • Renal 40%	• Substrate of CYP3A4, 2C9, 2C19 • Concentrated reduced by carbamazepine, fos-/phenytoin, phenobarbital • Carbamazepine increased AV blocking	• PR prolongation • Heart block, asystole reported • Hypotension	• Avoid if underlying heart disease • Caution if other AV-blocking drugs • Consider dose reduction if CrCl < 300 mg/day or hepatic impairment

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TABLE 1 (Continued)

Drug	Dose	Mechanism of action	Metabolism	Interactions	Adverse effects	Considerations for older adults
Levetiracetam	• LD: 60 mg/kg • Max: 4500 mg • MD: 750–2000 mg BID	• Inhibits SV2A-mediated vesicle release	• Renal	• No significant drug–drug interactions	• Sedation • Irritability	• Dose reduction if renal impairment or severe hepatic impairment • Half-life prolonged in older adults, due to decrease in GFR
Valproic acid	• LD: 40 mg/kg • Max: 3000 mg • MD: 15 mg/kg/day in 2–3 divided doses	• VGSC inhibition, augmentation of GABA, mild T-type Ca^{2+} current inhibition	• Hepatic metabolism	• Inhibits: CYP2C19, 2A6, 3A4 • Induces CYP2A6 • Concentration reduced by barbiturates and carbapenems • Increases concentration of carbamazepine, barbiturates, phenytoin, lamotrigine	• Hyperammonemia • Pancreatitis • Thrombocytopenia	• Minimal hypotension seen in older adults, but may need a slower infusion rate • Half-life doubled in older adults
Phenobarbital	• LD: 20 mg/kg • Max 2000 mg • MD: 1–3 mg/kg/day in 2–3 divided doses	• Binds to $GABA_AR$, prolongs Cl^- channel opening	• Hepatic 75% • Renal 25%	• Induces UGT, CYP3A4, 2B6, 2C9, 2A6, 1A2 • Induced by carbamazepine • Concentration increased by fos-/phenytoin, valproic acid	• Hypotension • Respiratory depression • Metabolic acidosis • Contains propylene glycol (IV)	• Reduced clearance in older adults
Third line: CIVADs						
Propofol	• IV load 1–2 mg/kg • Infusion: 30–200 μg/kg/min	• $GABA_AR$ agonist, NMDAR blockade	• Hepatic metabolism	• None	• PRIS (metabolic acidosis, bradycardia, rhabdomyolysis, cardiac arrest) • Hypotension • Myocardial depression • Hypertriglyceridemia	• Accumulates in adipose; consider using lean body weight to dose • Lower doses needed for sedation • Increased risk for hypotension, especially in patients with preexisting heart disease

(Continues)

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TABLE 1 (Continued)

Drug	Dose	Mechanism of action	Metabolism	Interactions	Adverse effects	Considerations for older adults
Midazolam	• IV load: .2 mg/kg • Infusion: .2–2.9 mg/kg/h	• See benzodiazepines	• Hepatic metabolism • Active metabolite undergoes renal excretion	• Increased half-life	• Hypotension • Respiratory depression • Accumulate with repeated dosing • Tachyphylaxis	• Sedation achieved at lower doses • Decreased clearance • Accumulation in adipose tissue • Heavily protein bound
Ketamine	• IV load: 1.5 mg/kg • Infusion: 1.2–7.5 mg/kg/h	• Noncompetitive NMDAR antagonist	• Hepatic metabolism	• Substrate of CYP2B6, 2C9, 3A4 • Induced by carbamazepine, fos-/phenytoin, phenobarbital	• Hypertension • Myocardial depression in patients with heart disease • Increased secretions • Laryngospasm • Cholestatic hepatotoxicity	• Caution in patients with cardiac disease • Reports of use in nonintubated patients
Barbiturates, e.g., pentobarbital	• IV load: 5–15 mg/kg • Infusion: .5–5 mg/kg/h	• See phenobarbital	• Hepatic metabolism	• Inducer of CYP3A4, A6 • Valproic acid may increase concentration	• Hypotension • Ileus • Myocardial depression, hypotension • Thrombocytopenia • Metabolic acidosis • Respiratory failure • Complete loss of neurological function • Contains propylene glycol	• Older adults more sensitive to hypotension and respiratory depression • Lower doses needed for EEG suppression
Third/fourth line: adjunctive ASMs						
Perampanel	• 12-mg load • 8–12 mg daily	• AMPAR glutamate noncompetitive inhibitor	• Hepatic metabolism	• Induced by CYP3A4 • Concentration decreased by carbamazepine, fos-/phenytoin, phenobarbital	• Irritability • Psychiatric symptoms	• Well tolerated in older adults with chronic epilepsy (15% discontinuation), most often discontinued due to psychiatric symptoms (8.7%) • Caution in patients with renal or hepatic impairment

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TABLE 1 (Continued)

Drug	Dose	Mechanism of action	Metabolism	Interactions	Adverse effects	Considerations for older adults
Topiramate	• LD: 200–400 mg NG/PO only • MD: 300–1600 mg/day in 2–4 divided doses	• Blocks VGSC, enhanced GABA transmission, NMDAR antagonist, mild carbonic anhydrase inhibitor	• Renal 70%	• Induces CYP3A4 • Inhibits CYP2C19 • Induced by carbamazepine • Concentration reduced by fos-/phenytoin • May enhance hyperammonemia, hepatic dysfunction, and hypothermia associated with valproic acid	• Nephrolithiasis (chronic) • Metabolic acidosis • Pancreatitis • Hyperammonemia • Acute angle-closure glaucoma	• Potential decreased benefit in older adults • Unclear whether older adults are more susceptible to cognitive and balance-related symptoms • Half-life varies with age
Clobazam	• Start 5 mg/day, increase to 40 mg/day	• See benzodiazepines	• Hepatic metabolism	• Induced by CYP2C19 and 3A4 • Concentration reduced by CYP2C19 inducers	• Sedation • DRESS	• Prolonged half-life in older adults • Decreased clearance in older men • Reduce dose in CYP2C19 poor metabolizers
Pregabalin, gabapentin	• Gabapentin: 300–1200 mg TID • Pregabalin: 150–600 mg daily in divided doses	• Inhibits release of excitatory neurotransmitters, binds to α2δ subunits of voltage-activated calcium channels	• Renal excretion	• Not affected by CYP inhibitors. Does not induce or inhibit CYP	• Sedation • Myoclonus • High risk for withdrawal seizures	• Reduced clearance in older adults, especially with renal impairment • "Nonresponders" more often older
Brivaracetam	• LD: 50–400 mg • MD: 50–200 mg BID	• See levetiracetam	• Hepatic metabolism	• Substrate of CYP2C19 • Reduced clearance by CYP2C19 inducers	• Somnolence • Agitation	• Unknown
Oxcarbazepine	• 600–2400 mg daily, in 2–3 divided doses	• Blocks VGSC	• Hepatic metabolism	• Not affected by CYP3A4 inducers • Mild inducer of CYP3A4, 2C19	• Hyponatremia • Exacerbation of myoclonus • Liver injury	• Hyponatremia risk higher in older adults • Avoid in patients with HLA-B*1502 allele

Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ASM, antiseizure medication; AV, atrioventricular; BID, twice daily; CIVAD, continuous intravenous anesthetic drug; Cl^-, chloride; CrCl, creatinine clearance; CYP, cytochrome P450; DRESS, drug rash with eosinophilia and systemic symptoms; EEG, electroencephalographic; GABA, γ-aminobutyric acid; $GABA_AR$, GABA type A receptor; GFR, glomerular filtration rate; IM, intramuscular; IN, intranasal; IV, intravenous; LD, loading dose; MD, maintenance dose; NG, nasogastric; NMDAR, N-methyl-D-aspartate receptor; PE, phenytoin equivalent; PO, per os; PR, per rectum; PRIS, propofol-related infusion syndrome; SV2A, synaptic vesicle protein 2; TID, three times daily; UGT, uridine 5′-diphospho-glucuronosyltransferase; VGSC, voltage-gated sodium channel.

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TABLE 2 Studies of first-line therapies.

Study	Total study population, *N*	Population age, years	Key findings	Participants ≥65 years old	Age-stratified analyses	Key findings in older adult population	Study limitations
VA cooperative study LRZ (.1 mg/kg) PHT (18 mg/kg) PB (15 mg/kg) DZP + PHT (.15 and 18 mg/kg)	518 (384 overt SE, 134 subtle SE)	Inclusion: ≥18 Mean: 59.5 Overt: 58.6 ± 15.6 Subtle: 62.0 ± 15.1	LRZ superior to PHT for SE cessation, no difference vs. PB or DZP + PHT	Overt: 43.5% ($n = 167$) Subtle: 51.5% ($n = 69$)	Yes	Similar response rate to whole cohort, though statistics not reported	Few females, delayed treatment, inclusion of postanoxic SE, variable treatment before study drug
PHTSE LRZ (2 mg) DZP (5 mg) Placebo	205	Inclusion: ≥18 Study: 50.8 LRZ: 49.9 ± 20.1 DZP: 50.4 ± 19.1 Placebo: 52 ± 18.2	LRZ, DZP increased SE cessation vs. placebo More cardiopulmonary complications in placebo vs. LRZ/DZP	$n = 47$ LRZ: 22.6% DZP: 22.2% Placebo: 23.8%	No	None published	Lower doses of LRZ/DZP used
RAMPART IV LRZ (4 mg) IM MDZ (10 mg)	893	Inclusion: all ages Mean: 44 MDZ: 43 ± 22 LRZ: 44 ± 22	Intramuscular MDZ is at least as safe and effective as intravenous LRZ	15.9% ($n = 142/1023$ randomized)	No	None published	Unknown whether drug or route of administration was superior given study design

Abbreviations: DZP, diazepam; IM, intramuscular; IV, intravenous; LRZ, lorazepam; PB, phenobarbital; PHT, phenytoin; PHTSE, Pre-Hospital Treatment of Status Epilepticus Trial; RAMPART, Rapid Anticonvulsant Medication Prior to Arrival Trial; SE, status epilepticus; VA: Veterans Affairs.

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may be associated with increased risk of intubation.[34–36] Furthermore, functional outcomes at hospital discharge are worse in patients for whom benzodiazepines are underdosed.[37]

6.1.1 | Age-related changes in benzodiazepine metabolism

Lorazepam metabolism occurs largely through hepatic conjugation, followed predominantly by renal excretion of lorazepam glucuronide. One study evaluating 15 older adults (60–84 years) and 15 younger adults (19–38 years) determined that elimination half-life did not differ following 1.5–3 mg of intravenous lorazepam, although total clearance was 22% less in the older group.[38] Midazolam undergoes metabolism through liver and intestinal CYP3A4 enzymes to a major active metabolite, 1-hydroxy midazolam, as well as less potent minor metabolites, 4-hydroxy midazolam and 1,4-dihydroxy midazolam. Based on limited pharmacokinetic studies of midazolam comparing younger and older adults, intravenous or intramuscular midazolam clearance seems to be decreased by 25% in older adults.[39] The half-life of diazepam and its major metabolite, desmethyldiazepam, linearly increases with age, from 20 h at 20 years of age to 90 h at 80 years of age.[40] Furthermore, reduced doses of intravenous diazepam resulted in similar levels of central nervous system depression when compared to younger counterparts.[41] Parenteral clonazepam, used as first-line treatment in Europe and parts of South America and Asia, undergoes significant phase I metabolism in the liver, thus older adults may experience similar delayed clearance as seen in midazolam and diazepam.[42] Hence, the treatment requirements of patients experiencing SE may differ, warranting treatment individualization.

Physiological changes in aging reduce GABA and glutamate functionality, but the impact of this on the treatment of SE remains unclear.[43] Although concern regarding the efficacy of benzodiazepines in the elderly may be reasonable, insufficient evidence exists to provide alternative initial dosing recommendations when treating elderly patients experiencing SE. Available data do not account for increased side effect sensitivity experienced by older adults. As previously noted, the importance of pharmacodynamic changes may outweigh pharmacokinetic alterations.[44] Given the pharmacodynamics and pharmacokinetics, lorazepam may be favorable, particularly in patients with established intravenous access. Clinicians must be aware of the extended effect of even single doses of benzodiazepines in older adults. Chronic benzodiazepine use is associated with increased risk of dementia and all-cause mortality, suggesting increased risk of this medication class.[45] Benzodiazepines reduce the risk for respiratory compromise in the prehospital setting, although it was not examined whether this is conferred to older adults.[31] It is possible that older patients receive smaller individual or cumulative doses of benzodiazepines given concern for complications. Although post hoc analyses of the ESETT cohort show undertreatment is common, their analyses were limited to a comparison between adults and children. Better understanding of the association between underdosing of benzodiazepines, the likelihood of benzodiazepine response, and associated complications are needed, particularly in the elderly.

6.2 | Antiseizure medications

As discussed previously, the VA cooperative study (including 236 patients 65 years and older) randomized participants to phenobarbital monotherapy, PHT monotherapy, or diazepam plus PHT.[29] No differences in seizure cessation were detected across these three treatment arms, although a post hoc analysis of adults aged ≥65 years found a higher response to phenobarbital (71.4%) than PHT (41.5%) for patients with GCSE (no *p*-value reported). Most subsequent studies were single-center trials, comparing two ASMs in patients with GCSE (Table 3). Differences in dosing strategies, populations, and study designs limit direct comparison.[26,46–48] A single trial conducted exclusively in older adults showed similar efficacy and safety between levetiracetam (68.3%) and valproic acid (74.1%) for adults 60 years and older with benzodiazepine-refractory SE.[26] ESETT randomized 384 patients, including 51 (13.3%) aged ≥65 years, to levetiracetam, fosphenytoin, or valproic acid following unsuccessful treatment with at least 4 mg of lorazepam or 10 mg of midazolam. GCSE cessation was assessed clinically, based on improving level of arousal.[49] A subgroup analysis of older adults found comparable efficacy (levetiracetam 37%, fosphenytoin 35%, valproic acid 47%). Among age groups (<18, 18–65, ≥65 years), seizure recurrence was most likely in the ≥65 group.[50] Importantly, EEG was not routinely employed, thus it is unclear whether treatment failure was driven by postictal coma or ESz and ESE.

An important randomized multicenter trial of adults 65 years and older comparing 30 mg/kg intravenous valproic acid and 45 mg/kg intravenous levetiracetam for benzodiazepine-resistant SE with a primary outcome of seizure cessation and control for 60 min following administration is currently enrolling subjects (German Clinical Trials Register: DRKS00022308).[27] EEG data collection is standardized, offering greater sensitivity for ESz and ESE detection following cessation of GCSE. There are several important considerations, including the use of lower doses

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TABLE 3 Studies of second-line therapies.

Study	Total study population, *N*	Population age, years	Key findings	Participants ≥65 years old	Age-stratified analyses	Key findings in older adult population	Study limitations
ESETT LEV: 60 mg/kg fPHT: 20 mg/kg VPA: 40 mg/kg	384	Inclusion: ≥2 Range: 1–94 Mean: 32.8 LEV: 33.3 ± 26.0 fPHT: 32.8 ± 25.4 VPA: 32.2 ± 25.4	LEV (47%), fPHT (45%), VPA (46%) have comparable efficacy treating established SE	*n* = 51 LEV, *n* = 19 fPHT, *n* = 17 VPA, *n* = 15	Yes	Lower efficacy: LEV (37%), fPHT (35%), VPA (47%) not statistically significant	No EEG confirmation of SE cessation; many BZD dosing protocol deviations
Su PB: 20 mg/kg load, 100 mg q6h VPA: 30 mg/kg load, 1–2 mg/kg/min infusion	69 PB: 33 VPA: 36	Mean: 43 ± 20 Range: 18–82	Higher SE termination in PB (84.8%) vs. VPA (63.9%); no difference in NCSE, relapse; more adverse events in PB group (30.3% vs. 16.7%)	13.6% (*n* ~ 9)	No	Not published	Alternate VPA dosing regimen makes comparison to other studies difficult; SE cessation much higher than ESETT
Misra PHT: 18 mg/kg VPA: 30 mg/kg	68 PHT: 33 VPA: 35	Range: 1–85 Mean/median not reported	VPA more effective than PHT as 1st (66% vs. 42%) and 2nd line (79% vs. 25%)	Unknown	No	Not published	SE defined as 10 min of convulsions, single center
Gilad PHT: 18 mg/kg VPA: 30 mg/kg	74 PHT: 25 (SE: 9, RSz: 16) VPA: 49 (SE: 18, RSz: 31)	Inclusion: ≥18 Mean: 53.3 PHT: 51 ± 12 VPA: 54.4 ± 20	Comparable SE control in VPA (87.8%) and PHT (88%); higher control in patients with RSz vs. SE	23.8% PHT: *n* ~ 3 VPA: *n* ~ 15	No	Not published	Included repetitive seizures and SE, SE defined as >30 min of convulsions, single center
Nene LRZ: .1 mg/kg + VPA or LEV: 20–25 mg/kg	118 VPA: 58 LEV: 60	Inclusion: ≥60 Mean: 67.6 VPA: 66.6 ± 6.7 LEV: 68.5 ± 8.0	Comparable SE control in VPA (68.3%) and LEV (74.1%)	All participants ≥60 years old	N/A	N/A	Single center, single blinded, lower doses used, no EEG endpoint
ToSEE LEV: 45 mg/kg VPA: 30 mg/kg	477 (planned)	Inclusion: ≥65	Primary endpoint: ictal cessation 15 min after the start of infusion persisting for the following 45 min of observation with EEG	All participants	Only recruiting age ≥65 years	Pending study completion	Lower doses of LEV and VPA, inclusion of GCSE and NCSE may limit power
TRENdS LAC: 400 mg vs. fPHT: 20 mg/kg PE	74 LAC = 37 fPHT = 37	Inclusion: Mean: 63.6 ± 16.6	LAC noninferior to fPHT in treating ESz (RR no ESz recurrence = 1.27 95% CI [.88–1.83])	46.6% (*n* ~ 34)	No	Not published	ESE not enrolled; frequent crossover, variable ASMs used prior to enrollment

Abbreviations: ASM, antiseizure medication; BZD, benzodiazepine; CI, confidence interval; EEG, electroencephalographic; ESE, electrographic SE; ESETT, Established Status Epilepticus Treatment Trial; ESz, electrographic seizures; fPHT, fosphenytoin; GCSE, generalized convulsive SE; LAC, lacosamide; LEV, levetiracetam; LRZ, lorazepam; N/A, not available; NCSE, nonconvulsive SE; PB, phenobarbital; PE, phenytoin equivalent; PHT, phenytoin; q6h, every 6 h; RR, relative risk; RSz, repetitive seizures; SE, status epilepticus; TRENdS, Treatment of Recurrent Electrographic Nonconvulsive Seizures; VPA, valproic acid.

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of levetiracetam and valproic acid than in ESETT as well as lower doses of benzodiazepines to meet inclusion criteria (2 mg lorazepam, 5 mg midazolam, 5 mg diazepam, 1 mg intravenous clonazepam). The study will recruit patients with GCSE and ESE, which may provide evidence to guide treatment of ESE, which may be more prevalent in older adults.

Data on other ASMs in established SE is limited. Lacosamide was compared to valproic acid in an open-label pilot study of 66 participants, median age 40 years, with similar efficacy.[51] For ESz, a trial of 74 subjects, 65% of whom were ≥60 years old, lacosamide was noninferior to PHT with similar tolerability, although patients with ESE were not enrolled.[52] A recent single-center randomized controlled trial (RCT) comparing phenobarbital and valproic acid showed similar efficacy as second-line treatment for SE and a significant ordinal shift in modified Rankin scale score at 3 and 12 months favoring phenobarbital, although only 10% of participants were ≥65 years old. Collection of long-term and patient-centered outcomes in this trial is unique.[53]

6.2.1 | Age-related changes in metabolism

Fosphenytoin/PHT, valproic acid, and phenobarbital have a high affinity for albumin binding. For PHT and fosphenytoin specifically, patients >60 years of age have reduced metabolism as well as lower saturation of metabolic pathways at lower concentrations, increasing the risk for toxicity, thus necessitating smaller doses.[54,55] Compounding these challenges, as renal function declines with age, free PHT excretion may also be impaired.[56] For valproic acid, the elimination half-life doubles to 14.9 h in older adults, although this likely reflects increased volume distribution rather than a change in clearance. The clearance of phenobarbital is reduced in older adults, likely through alterations in either hepatic or renal elimination.[57] Levetiracetam's half-life is extended to 10–11 h in older adults, likely due to alterations in renal function; resultantly, maintenance doses are suggested.[58] There is increased risk of hypotension and cardiac conduction abnormalities with sodium channel blockers, especially PHT. Lacosamide is associated with an increased risk of PR prolongation in older adults with underlying cardiac diseases.[59] Older adults tolerate loading doses of valproic acid with minimal hemodynamic instability; however, the rate may need to be slowed to deliver the full loading dose, as was done in 158 of 159 infusions in prior studies.[8] Fosphenytoin can be administered more safely than PHT and can be administered intramuscularly, although it still warrants blood pressure and cardiac monitoring.[60]

Treatment of GCSE with an ASM following benzodiazepine is well supported; however, important questions remain. For older adults presenting with benzodiazepine-refractory SE, a preferred ASM is not established. Furthermore, given recognized changes in drug metabolism in older adults, it is unclear whether current dosing strategies are most appropriate and whether older adults are at greater risk for toxicities associated with ASMs. In addition, scant evidence exists to guide management of ESE, thus treatment typically is extrapolated from GCSE treatment algorithms. However, given the heterogeneity of etiologies seen in ESE across critically ill patients, best treatment strategies need to be further elucidated, particularly in older adults in whom avoidance of oversedation and mechanical ventilation are preferable due to their association with poor outcomes.[61,62] We suggest the clinician pay particular attention to medical comorbidities, including renal and hepatic function, cardiac history, and presence of arrhythmias (including bradyarrhythmias) when selecting an ASM. Furthermore, clinicians should be aware of cumulative sedating effects of multiple ASMs, which may necessitate airway protection.

6.3 | Continuous intravenous anesthetic drugs

In this section, we discuss evidence regarding propofol, midazolam, ketamine, and barbiturates for RSE. Practice patterns and guidelines vary regarding timing of initiation of a CIVAD for RSE.[35,63,64] Evidence supporting CIVAD use is predominantly retrospective and uncontrolled, thus there is significant equipoise in agent and dosing. Furthermore, there is scant evidence regarding CIVAD use in focal SE and ESE, particularly in older adults. After review, we did not identify any studies dedicated to older adults with RSE, nor any subgroup analyses stratifying by patient age in the existing literature.

6.3.1 | Efficacy

There are limited prospective data to compare the efficacy of CIVADs, although based on RCT and retrospective data, RSE control appears similar between propofol, midazolam, and barbiturates. Given sample size and lack of subgroup analyses, insight into efficacy for older adults is limited.[65–68] Ketamine and barbiturates are rarely used as a first choice CIVAD for SE and are more often considered adjunctive therapies.[35] Most data evaluating ketamine come from large series without control groups, although with reasonable inclusion of older adults (25%–50%).[69,70] Efficacy in superrefractory

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SE (SRSE) ranges from 27% to 91% when combined with midazolam or propofol, although definitions for treatment success varied.[71,72] A recent series of patients with RSE treated with ketamine infusion without endotracheal intubation demonstrated 71% RSE resolution, including nine of 13 aged ≥65 years.[73] Avoidance of mechanical ventilation may be particularly desirable for older adults, although this approach requires further study.

6.3.2 | Pharmacokinetics and pharmacodynamics

Propofol undergoes significant extrahepatic clearance with decreased drug clearance and volumes of distribution in older adults.[74] Older adults require lower doses to induce loss of consciousness, whereas increased doses are associated with more hemodynamic effects.[75] Clinicians may consider the use of lean body weight to calculate induction doses due to age-related changes in body composition, especially for bolus doses or rapid escalation of infusions, which are commonly employed in RSE.[76]

Compared to a single-dose of midazolam, continuous midazolam infusions exhibit wide intra- and interpatient pharmacodynamic variability, with half-life increasing in older adults, especially older men.[77,78] Older adults required lower doses to induce clinical sedation and EEG suppression, although no differences in pharmacokinetics were identified.[39] Active metabolites may persist for an extended period after cessation of midazolam continuous infusions, particularly in patients with renal dysfunction, which is of concern due to age-related reduction in renal clearance.[79]

Data on pharmacokinetic and pharmacodynamic changes of ketamine metabolism with age are lacking. Ketamine exhibits low plasma protein binding and has a high volume of distribution. Modest reductions in ketamine clearance have been identified in renal impairment, with hepatic metabolism being mostly dependent on hepatic blood flow and not intrinsic clearance.[80] Ketamine appears to have a neutral effect on intracranial pressure, cerebral blood flow, mean arterial pressure, and cerebral perfusion pressure as well as reduced need for vasopressor support.[81]

Thiopentone has sedating effects at lower doses in the elderly, longer half-life, less distribution, and greater decreases in cardiac output.[82] The dose of thiopentone required to achieve burst suppression on EEG also decreases linearly with age, likely due to changes in volume of distribution rather than increased sensitivity to the drug, although reports are inconsistent.[83,84]

6.3.3 | Safety and tolerability

Propofol-related infusion syndrome (PRIS) is most often reported in younger adults; however, increasing age does not appear to be protective. The mean age of adult cases appears to be increasing over time.[85] Risk factors for PRIS, including critical illness, vasopressor use, glucocorticoid use, and carbohydrate depletion, are common in older adults with RSE.[86] Furthermore, PRIS is associated with higher doses and longer durations of therapy, both common in the treatment of RSE.[87] Propofol-induced hypotension may be exaggerated due to increased susceptibility to reduced sympathetic outflow, increased vasodilation, and reduction in myocardial contractility in older adults, particularly those with preexisting cardiovascular disease.[88] Midazolam may be favorable over barbiturates such as sodium thiopental given comparable efficacy but association with briefer intensive care unit length of stay, better 6-month GOS-Extended, and lower rates of hypotension requiring vasopressors, infections, anemia requiring transfusion, leukopenia, and hyponatremia, although some of these effects may be driven by significantly higher rates of burst suppression in the sodium thiopental group in that study.[89] Additionally, midazolam may impair immune system function, which could act synergistically with age-related changes in the immune system, increasing the risk for infectious complications in older adults.[90] Ketamine is associated with a dose-dependent increase in heart rate and blood pressure, which may reduce hypotension, but could carry risk in patients with coronary artery disease and hypertension.[91] At sedative doses (lower than RSE), cardiovascular response was variable, with 24% developing hypertension and 23.5% developing hypotension, although few participants were older.[92] Compared to other CIVADs, barbiturates are associated with an increased risk of hypotension and prolonged mechanical ventilation.[66,68]

6.3.4 | Special considerations for older adults

Evidence to guide selection between anesthetic agents is lacking for all patients, especially older adults. Our understanding of drug metabolism and safety in RSE is limited, given that information is derived from studies examining use as sedation for surgical procedures or for critically ill patients in intensive care units, where lower doses and/or shorter exposures may provide discrepant information. Given the risks of complications in older adults treated with CIVADs, clinicians should weigh the risks and benefits of aggressive treatment and engage in shared medical decision-making with surrogates and may consider

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additional ASM trials before initiating a CIVAD, particularly in cases of focal SE and ESE. Potentially important factors to consider in such cases are detailed in Figure 2. When selecting a CIVAD, ketamine may be preferable given emerging evidence of use without mechanical ventilation as well as favorable hemodynamics, whereas barbiturates may be considered as later line CIVADs given their substantial side effect profile.

6.4 | Adjunctive treatments

Adjunctive therapies have been used in RSE and SRSE, including ASMs, immunotherapy, diet-based therapies, electroconvulsive therapy, hypothermia, and inhaled anesthetics. Although these treatments may be appealing to avoid the need for mechanical ventilation and CIVAD use, lack of high-quality data limits their utility.[93] As such, interventions may be considered case by case, factoring etiology, comorbidities, and any limitations in care based on advanced directives.

6.4.1 | Additional ASMs

Additional ASMs, including phenobarbital, perampanel, topiramate, pregabalin, clobazam, and brivaracetam, may have a role in management of SRSE, although evidence pertaining to older adults is negligible. Safety and efficacy are extrapolated from chronic use managing epilepsy and are detailed in Table 1. Phenobarbital is widely used as a second-line agent in low-to-middle income countries.[94] In SRSE, adjunctive phenobarbital may be beneficial, particularly when higher serum levels are achieved, although increasing age is associated with treatment failure in multivariable models.[95] Data for rufinamide, eslicarbazepine, stiripentol, cannabidiol, and zonisamide in SE are sparse.[96,97]

6.4.2 | Immune-modulating therapies

Immunotherapy, including high-dose intravenous steroids, plasmapheresis, intravenous immunoglobulin (IVIG), and anti-interleukin drugs, can be considered in RSE and SRSE. Reported use of adjuvant steroids ranges widely depending on the cohort (1.5%–39%) and may reflect differing approaches across institutions and/or regions. A large systematic review of adjunctive steroid use is lacking.[35,97] Plasmapheresis and IVIG in patients with RSE may have some moderate efficacy, although only one of six patients 60 years or older improved, compared to 45%–52% of all patients included.[98,99] Minor complications related to plasmapheresis may be more common in older patients, whereas the safety profile of IVIG appears similar, although higher occurrence of comorbidities such as kidney disease in older adults may present challenges in implementing these treatments.[100,101]

6.4.3 | Dietary therapy

KD and modified Atkins diet (MAD) have been used increasingly to manage RSE and SRSE. Retrospective and prospective open-label studies, including 36 patients ($n = 6$

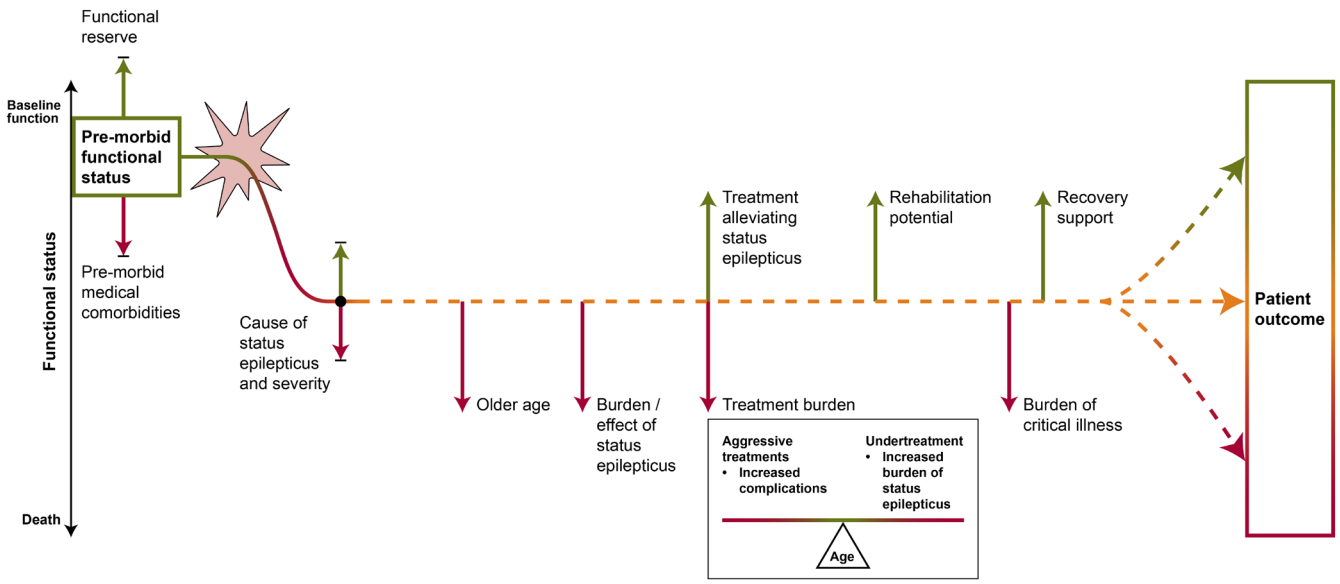

FIGURE 2 Schematic of key factors influencing outcomes for older adults with status epilepticus that clinicians should consider during management. Artwork by T.I.W. (2025).

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≥65 years old) with SRSE, suggested achieving ketosis is feasible. Five of six older adults achieved ketosis, and four had eventual resolution of SRSE.[28,102,103] Challenges to KD include concomitant medications that may present safety concerns, for example, propofol (PRIS) and topiramate (metabolic acidosis), as well as drugs that will prevent ketosis. Osteopenia and osteoporosis are complications of greater concern in older adults; however, in short-term use of KD/MAD the risk may be lower.[104] Older adults in the outpatient setting have been shown to tolerate long-term use of KD for a variety of indications, with a 15% incidence of KD-related complications (most commonly dyslipidemia, constipation, and low international normalized ratio).[105] Furthermore, KD has been shown to be feasible and tolerable in older adults with other neurological diseases, such as Alzheimer disease.[106] However, less is known regarding the tolerability of KD and MAD in critically ill older adults.

6.4.4 | Other therapies

Hypothermia has been shown to induce electrocortical silence and thus has been considered a potential adjunct for SE; however, a large RCT, randomizing intubated patients with SE to standard of care with or without therapeutic hypothermia to 32°C–34°C did not show benefit in progression to RSE and SRSE, or in 90-day outcomes. A secondary analysis suggested lower likelihood of benefit in participants older than 65 years.[107] Other therapies including inhaled anesthetics, transcranial magnetic stimulation, and neuromodulatory devices have been reported, but rarely in adults aged ≥65 years.[108,109] Pyridoxine deficiencies have been reported in SE, but supplementation has not adequately been studied.[110] Case reports and series have described the use of electroconvulsive therapy in patients with SRSE with moderate efficacy and good safety, including patients 65 years and older.[111] Adverse effects in older adults, extrapolated from psychiatry literature, include memory loss, headache, fatigue, and nausea/vomiting, although evidence regarding cognitive effects is conflicting.[112]

Given the high morbidity and mortality in RSE, SRSE, and new onset RSE, particularly among older adults, novel treatments are appealing. Diet therapy appears to be safe, well tolerated, and efficacious. Use of adjunctive therapies could potentially reduce the dose and duration of CIVADs; however, well-designed prospective studies are needed to better evaluate these approaches. We suggest that clinicians consider the use of adjunctive therapies, particularly diet therapy, in select cases of RSE and SRSE.

7 | OUTCOMES AND PROGNOSTICATION

Multiple factors are important for understanding prognosis following SE. First, there is higher morbidity and mortality associated with increasing refractoriness to treatment, with reports of 4.2%, 14.9%, and 37.9% mortality in adults with SE, RSE, and SRSE, respectively.[113] This risk is higher in adults older than 65 years, with 8.7%, 21.6%, and 43.1% mortality in SE, RSE, and SRSE, respectively. Likewise, age ≥65 years is associated with an increased odds of mortality as high as 3.97.[114] Among older adults with SE, mortality increases with age: 65–75 (19%), 75–85 (23%), >85 years (24.1%).[10] Temporal trends suggest an increase in SE hospitalizations but stagnant case fatality rate over the past 2 decades, despite significant changes in definitions to promote earlier treatment and a growing body of evidence to guide management.[115] However, temporal trends for older adults with SE are unknown. Age is integrated into two well-recognized clinical grading tools in SE, the Status Epilepticus Severity Score (STESS) and the Epidemiology-Based Mortality Score in Status Epilepticus (EMSE), where increasing age was associated with mortality in both; however, the EMSE may outperform STESS in predicting mortality risk for patients aged ≥60 years.[116,117] Remaining questions are how differences in etiology of SE in older adults, burden of medical comorbidities, increased susceptibility to complications, or increased withdrawal of life-sustaining therapies (WLST) are associated with worse mortality.

Etiologies common in older adults, such as acute and remote ischemic stroke, trauma, and hemorrhagic stroke, are associated with high mortality.[10] Thus, differences in etiology of SE across the lifespan likely influence the increased mortality associated with advancing age. WLST is often the proximal cause of death in acute brain injury, and is an important final cause of death in patients with SE.[118] Unfortunately, many studies on SE lack details of cause of death.[61] In critical illness, older age is associated with increased likelihood of initiating limitations in life-sustaining treatments including ventilator support, surgeries, and dialysis.[119] Furthermore, physicians may underestimate older adults' wishes for ongoing care.[120] Age is less clearly a factor in decisions surrounding WLST due to perceived poor neurological prognosis.[121] To date, no study has investigated the association between age and WLST due to perceived poor neurological prognosis specifically in SE. For survivors of SE, risk of mortality increases over the 2–3 years following an SE episode, then levels off. Advancing age, etiology, and refractoriness of SE are important factors

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TABLE 4 Treatment considerations for status epilepticus in older adults.

Benzodiazepines	• In the absence of evidence evaluating dose modification in older adults, follow NCS/AES dosing guidelines • Consider that significant sarcopenia could reduce bioavailability of intramuscular midazolam • Recognize that decreased clearance and longer half-life may lead to longer sedation, especially in the setting of multiple doses or in drugs with significant hepatic oxidative metabolism (e.g., midazolam, diazepam, clonazepam)
Nonbenzodiazepine ASMs	• Consider comorbid conditions when selecting ASMs, including comorbidities (renal and hepatic dysfunction, cardiac history, arrhythmias) • Less sedating medications may be preferable to more sedating ASMs • Be aware of possible cumulative sedating effect of multiple ASMs
CIVADs	• Consider trialing additional ASM load(s) before initiating CIVAD especially in cases of focal SE, ESE, or repetitive seizures with adequate airway protection or limitations in care (e.g., DNI) • Ketamine infusion without intubation may be a reasonable consideration on a case-by-case basis • Side effects of barbiturates may be exaggerated in older adults
Adjuncts	• Perampanel may be a less sedating adjunct ASM • Consider use of nonpharmacologic therapies, e.g., diet therapies
General considerations	• Patient-level factors, including medical comorbidities, level of baseline function, etiology of SE, and personal values (e.g., quality of life considerations that may drive limitations in care) should be taken into account when determining treatment approach • Be attentive to risks of both under- and overtreatment of SE • Utilization of GCSE treatment algorithms may not be appropriate for older adults with focal SE, repetitive seizures, or ESE

Abbreviations: AES, American Epilepsy Society; ASM, antiseizure medication; CIVAD, continuous intravenous anesthetic drug; DNI, do not intubate order; ESE, electrographic ES; GCSE, generalized convulsive SE; NCS, Neurocritical Care Society; SE, status epilepticus.

in long-term mortality following hospital discharge.[122] Survivors of SE are also at increased risk of cognitive impairment, including deficits in memory, learning, and executive function, suggesting hippocampal and frontal dysfunction.[123] Post-SE cognitive impairment and risk of dementia in older adults have not specifically been studied, but warrant investigation.

8 | CONCLUSIONS

Due to lack of specific evidence, SE is managed agnostically to patient age. However, there are important differences in etiology of SE and age-related pharmacodynamic and pharmacokinetic changes that could have meaningful implications for older adults with SE. Although RCTs have included older adults, they are underrepresented compared to the incidence of SE in this population. Studies of second- and third-line agents have been stopped early due to futility or slow recruitment, limiting the ability to appreciate potential differential treatment response and safety profile stratified by age. Algorithms for ESE management are often extrapolated from convulsive SE; however, significant differences exist between ESE and convulsive SE, including degree of neurotoxicity, duration before treatment initiation, refractoriness, and contributing/provoking factors, all of which may impact management decisions.

We have identified several considerations for the clinician caring for older adults with SE to help guide management decisions (Table 4). Moving forward, there are important questions that deserve further study, including the following: Should ASMs and CIVADs be dosed differently in older adults? Are older adults more sensitive to the detrimental effects of CIVADs? Consideration of potential treatment outcomes and their potential risks must be considered when selecting outcomes for clinical trials and when making real-time decisions in the bedside care of older adults with SE.

AUTHOR CONTRIBUTIONS

Matthew R. Woodward: Conceptualization; data curation; visualization; writing—original draft; writing—review and editing. **Michael J. Armahizer:** Data curation; writing—original draft; writing—review and editing. **Tina I. Wang:** Artwork. **Neeraj Badjatia:** Conceptualization; writing—review and editing. **Emily L. Johnson:** Conceptualization; writing—review and editing. **Emily J. Gilmore:** Conceptualization; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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